REMARKS

In the Office Action dated January 31, 2008, claims 1-16 are pending, claims 1-4 and 8-12 are rejected and claims 5-7 and 13-16 are withdrawn from consideration. Reconsideration is requested at least for the reasons discussed hereinbelow.

Claim 1 has been amended to correct the spelling of "dose." Claim 12 has been amended to insert the term "method" in place of the term "use" to conform to claims practice and also to correct a typographical error regarding "1.5".

The Examiner states that the restriction requirement is made final and that claims 5-7 and 13-16 are withdrawn from further consideration. However, the Examiner had required restriction between:

I. Claims 1-13, drawn to a method of treatment of portal hypertension, and

II. Claims 14-16, drawn to a pharmaceutical composition.

Applicants elected Group I, i.e., claims 1-13. Thus, only claims 14-16 should be withdrawn from further consideration.

Claim 12 is rejected under 35 USC § 101. It is submitted that the above amendment renders this rejection moot.

Claims 1-4 and 8-12 are rejected under 35 USC § 112, first paragraph. The Examiner asserts that the specification does not reasonably provide enablement for the **prevention** of portal hypertension and its bleeding complications. On the other hand, the Examiner acknowledges that the specification does enable for the **treatment** of portal hypertension and its bleeding complications.

The Examiner further notes that the prior art teaches that portal hypertension and its bleeding complications are difficult to treat and there is no known prevention. The Examiner further refers to de

Franchis et al. as teaching that all patients with cirrhosis of the liver will eventually develop portal hypertension and esphagogastric varices.

Applicants respectfully submit that, although the Examiner may be correct that, indeed, prior art teachings are hardly effective to treat portal hypertension and its bleeding complications, and that cirrhosis may translate into portal hypertension and bleeding complications, the Examiner's conclusion that the present application does not enable the claimed invention is erroneous.

The teachings of the **present application**, in fact, do provide an **effective treatment** of portal hypertension and bleeding complications, as credibly demonstrated by the example presented in the specification. These results provided by the present invention make a substantial difference over prior art teachings. Because the administration of PEE 5-inhibitors like Vardenafil display previously unexpected selectivity of significantly increased portal vein flow versa unaltered or even decreased arterial flow, which transforms into a substantially increased inflow of blood into and through the liver, an effective **prevention** of portal hypertension and bleeding complications of liver cirrhosis patients is provided. The effectivity and enablement for the prevention of portal hypertension and its bleeding complications cannot be reasonably doubted in view of the new findings in liver cirrhosis patients as described in the present specification.

Thus, it is requested that this rejection be withdrawn.

Claims 1-4 and 8-12 are rejected under 35 USC § 103(a) over Garcia et al ("CC") in view of Garcia-Tsao ("CU"), and further in view of Niazi et al. (U.S. 63338862). Applicants respectfully disagree.

The Examiner states that Garcia CU teaches that administration of Sildenafil at 10mg/kg decreases portal vein pressure. However, the Garcia CU abstract concludes that administration of Sildenafil provides an increase in PVF (portal venous flow) with no accompanying increase in PVP (portal venous pressure) [see last 4 lines of the abstract of Garcia CU].

Applicants strongly contest that Garcia may provide a reasonable expectation of success for treating portal hypertension or associated bleeding complications. The Garcia CU reference is briefly discussed in the present application (page 5, second paragraph).

First, Garcia does not deal at all with prevention or treatment of portal hypertension. Rather, following from the acknowledgement that patients with chronic liver disease often have erectile dysfunction (ED), the hemodynamic effects the conventional and typical use of Sildenafil to treat ED is investigated and reported in Garcia CU. Garcia CU fails to discuss liver cirrhoses, as such. Thus, Garcia CU is entirely silent about any possible therapeutic concept of using Sildenafil for the treatment of portal hypertension or its bleeding complications. By contrast, Garcia CU is concerned about increased portal venous inflow and possible worsened portal hypertension; thus, Garcia CU tested effects of Sildenafil on systemic and portal hemodynamics in normal rats, as a model for possible adverse effects which may appear when Sildenafil is used to treat ED in patients with chronic liver disease (see first 9 lines, particularly lines 5 to 9, of the abstract of Garcia CU).

Further, it is not seen how the results reported by Garcia CU would have led one of ordinary skill in the art to use Sildenafil or another PDE 5-inhibitor to treat portal hypertension or its bleeding complications. In case of administering i.v. doses of 0.1 and 1 mg/kg dose per rat some general decrease in systemic pressure (measured by the mean arterial pressure, MAP) was observed. However, Garcia CU concludes that increase in portal venous flow (PVF) was not **accompanied by a significant increase in portal venous pressure (PVP)**. Further, only in the event of administering an extreme and pathologic dose of 10 mg/kg per rat intravenously is there observed a dramatic drop of systemic pressure (MAP) by more than 50%. Such a dramatic drop of systemic pressure by more than 50% is an entirely non physiologic, unrealistic and unreasonable approach to see any therapeutic effect. In fact, Garcia CU, notes that although MAP returned towards baseline within 5 min. in the 0.1 and 1 mg/kg doses (however without observing any effect other than general systemic pressure decrease as noted shove), it is stated that the diminished MAP persisted with the 10 mg/kg i.v. dose. When the rats receiving the 10 mg/kg i.v. doses are knocked out by the drastic drop of systemic (MAP) pressure by more than

50%, it is self-evident that also portal venous pressure (PVP) drops, e. g., by 16.5% as reported by Garcia CU, **without however** providing any suggestion toward a therapeutic effect in the liver. In line with the overall results, Garcia CU states in the "Conclusions":

> The i.v. administration of Sildenafil produces profound peripheral vasodilatation. Although this causes mesenteric arterial dilation and an increase in PVF, there is **no accompanying increase in PVP** most likely due to a decreased resistance in the portal bed. *(Emphasis added.)*

Thus, in the absence of any contrary statement (and unlike situations where systemic pressure (MAP) is drastically decreased, which eventually would lead to lethal effects in the treated organism), Garcia CU ***fails*** to teach or suggest that Sildenafil may be active to decrease portal venous pressure of the rat liver. In line with this conclusion, Garcia CU is entirely silent about suggesting the use of Sildenafil for treating animals or humans in the case of portal hypertension originating, e. g., from liver cirrhoses. One of ordinary skill in the art would learn from Garcia CU that they are satisfied with the conclusions that, when patients are treated for ED, Sildenafil does not worsen portal hypertension.

It should be noted that the present specification makes clear that the adjustment of the dose shall be made depending on the mode of administration. That is, when an oral administration is chosen, a relatively high dose may still be appropriate (which may also depend on the activity of the PDE 5-inhibitor chosen). On the other hand, when it comes to intravenous (i.v.) administration, a relatively low dose is more appropriate. See, for example, page 10 to top of page 11 of the present specification.

Another relevant issue is that the surprising effects described in the present specification are not at all reasonably expected from the results described by Garcia CU. As discussed above, the effect of decreasing the **general systemic pressure** (determined by arterial blood pressure), and a senseless pathologic decrease of systematic pressure by more than 50% through extreme i.v. doses, ***is* insufficient** to provide any reasonable expectation for the effects described in the invention of the present specification that are causative for a successful treatment of portal hypertension and associated bleeding complications.

Applicants have discovered the surprisingly distinct selectivity of PDE 5-inhibitors on different types of vessels relevant for liver blood flow, which has not been recognized before the present invention. Although vessel resistivity of the arterial vessels supplying the liver remained unchanged or even increased (and, correspondingly, maintaining or decreasing **arterial** inflow to the liver), the **portal inflow** significantly increased **selectively**. Because arterial and portal blood inflow to the liver are respectively complementary, this selective effect seems causative for the surprising effectivity at the liver target site of patients affected *by* liver cirrhoses. See, page 8 second full paragraph of the present specification. Surprisingly and unexpectedly in view of the results reported by Garcia CU, this specific selectivity of a marked increase of portal vein flow discovered by Applicants versus almost unaffected arterial blood flow (measured in the 1st series of examples using Sildenafil by a portal vein flow increase of 32.5% and a resistivity index (RI) of A. Hepatica Communis of +4.48% and a RI of Truncus Coeliacus of even -1.5%) forms the key finding of the invention for the success of treating portal hypertension and its bleeding complications.

These effects in accord with the present invention have been further confirmed in 2nd series of examples using Vardinafil by studying volunteers and patients having portal hypertension with liver cirrhoses origin and, further, in additional investigations of patients having liver cirrhoses in Examples 3 and 4. Please see the description of the results on page 17, penultimate paragraph, on page 18, middle paragraph and on page 19 of the present specification.

Applicants respectfully submit that, a person skilled in the art and being unbiased, i. e., without knowing the present invention by hindsight, would never deduce or expect a successful treatment (or prevention) of portal hypertension or its bleeding complications in view of Garcia CU. Because already Garcia CU fails to teach or suggest the therapeutic concepts of the present invention in case of Sildenafil, this failure must apply even more to the case of Vardenafil, which compound is not discussed at all by Garcia CU.

Again, Applicants re-emphasize that Garcia CU does not teach or suggest, or give reasonable expectations on the **selective** activity of Sildenafil, Vardinafil or any other PDE 5-inhibitor on portal vein flow versus arterial vein flow into the liver, whereupon only this selective inflow substantially improves blood flow through the liver and, thus, alleviates liver cirrhoses symptoms and associated bleeding complications, as discussed in detail above.

The Examiner admits that Garcia CU fails to teach that the PDE 5-inhibitor-induced decreases in portal pressure treats bleeding complications of portal hypertension and cites Niazi and Garcia-Tsao to make up for the deficiency. However, neither Niazi nor Garcia-Tsao, nor their combination make up for the deficiencies of Garcia CU. First, as discussed above, Garcia CU only teaches that a pathological administration of Sildenafil will decrease PVP. Nothing in either Niazi or Garcia-Tsao suggest using a PDE 5-inhibitor to treat bleeding complications of portal hypertension.

Thus, it is not seen how the presently claimed invention would have been obvious to one of ordinary skill in the art in view of any combination of Garcia CU, Niazi and Garcia-Tsao.

In view of the discussion above, applicant respectfully submits that the pending application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, the Commissioner is hereby authorized and requested to charge Deposit Account No. **04-1105**.

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Respectfully submitted,

By _____

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